Retinoids for prevention and treatment of actinic keratosis*

Retinoides para a prevenção e tratamento das queratoses actínicas

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Abstract: Actinic keratosis is a common cause of dermatological consultations and it presents a strong association with squamous cell carcinoma. Many substances are used for treatment and prevention, such as retinoids. Nevertheless, many studies on retinoids emphasize their application in treating and preventing non melanoma skin cancers. In this article, we reviewed studies about systemic and topical retinoids used with immunocompetent patients and organ transplant recipients with actinic keratosis, as primary or secondary outcomes. The majority of these papers pointed to a reduction in actinic keratosis count after treatment with retinoids. However, studies need to be better-defined in order to address the lack of a standardized dose, the absence of control groups, the low number of patients and short follow-up periods. Blind, randomized and controlled clinical trials with adequate sample sizes, specifically focused on actinic keratosis, are needed to clarify the real benefit of topical and/or oral retinoids. Comparison of efficacy and safety between oral and topical retinoids in the prevention and treatment of non-melanoma skin cancers and actinic keratosis is an essential pre requisite to establish new strategies to control these conditions.
Keywords: Chemoprevention; Isotretinoin; Keratosis, Actinic; Retinoids; Tretinoin

Resumo: A queratose actínica é uma causa comum de consultas dermatológicas e apresenta forte associação com o carcinoma espinocelular. Muitas substâncias são utilizadas para seu tratamento e prevenção, assim como os retinoides. Entretanto, muitos estudos sobre retinoides salientam seu uso no tratamento e prevenção de cânceres de pele não melanoma. Neste artigo, nós revisamos estudos que avaliam o uso dos retinoides sistêmicos e tópicos para pacientes imunocompetentes e imunossuprimidos com queratoses actínicas, como desfechos primários e secundários. A maioria destes estudos mostra redução na contagem das queratoses actínicas após o tratamento com retinóides. Além disso, ajustes no delineamento dos estudos deveriam ser feitos quanto à falta de padronização da dose, ausência de grupos controle, número pequeno de pacientes e tempo curto de seguimento. Ensaios clínicos cegos, randomizados e controlados com tamanho amostral adequado tendo como alvo específico as queratoses actínicas são necessários para esclarecer o real benefício dos retinoides tópicos e/ou orais. A comparação da eficácia e segurança entre os retinoides orais e tópicos na prevenção e tratamento dos cânceres de pele não melanoma e queratoses actínicas é um pré-requisito essencial para o estabelecimento de novas estratégias para o controle destas condições.
Palavras-chave: Ceratose actínica; Isotretinoína; Quimioprevenção; Retinóides; Tretinoína

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INTRODUCTION

Actinic keratoses (AKs) are the third leading cause of dermatological consultations in the United States, the fourth in Brazil, and the first if one considers only patients aged over 65. [1,2]

AKs are mostly caused by non-ionizing radiation, i.e., chronic sun exposure (ultraviolet radiation - UV), they develop in sun-exposed areas and, if untreated, can progress to squamous cell carcinoma (SCC).[3] Therefore, they need specific treatment and various means are applied, such as curettage, electrosurgery, cryotherapy with liquid nitrogen, dermabrasion, chemical peels, 5-fluorouracil (5-FU), 3% diclofenac combined with 2.5 % hyaluronic acid in gel, 5% imiquimod cream, photodynamic therapy, topical and systemic retinoids. [5,4]

Retinoids are well-known and widely used for the prevention and treatment of non-melanoma skin cancers. This article reviews the most important studies on the use of topical and systemic retinoids for the treatment and prevention of AKs.

ACTION MECHANISM OF RETINOIDS IN CARCINOGENESIS

The relationship between retinoids and cancer dates from the 1920s when vitamin A deficiency was related to malignancies in rats.[6] Biochemical studies in the 1970s and 80s suggested that a relative deficiency of retinoid could be associated with epithelial cancers.[7] This idea was applied to AKs in 1962, when Von Stuttgen first used vitamin A acid for the treatment of AKs in three patients.[8,6,9] In 1982, Peck and colleagues published a landmark study using oral isotretinoin for chemoprevention of skin cancer in high risk patients. In 1988, Kraemer showed that high doses of oral isotretinoin (2mg/kg/day) was effective in preventing the development of skin cancer in five patients with xeroderma pigmentosum.[10,11]

The action mechanism of retinoids in the prevention and treatment of skin cancers has not yet been fully elucidated.[12] They are known to: have antiproliferative and anti-apoptotic properties; regulate the differentiation and growth of keratinocytes; interfere in the process of tumor initiation; reduce regulation of proto-oncogenes; increase the expression of p53 and pro-apoptotic caspases; and sensitize keratinocytes to apoptosis.[13,14,15] In murine models of skin carcinogenesis, retinoids target the B-Raf/Mek/Erk signaling pathway.[16] It is speculated that they have a role as an antioxidant, reducing the number of sunburn cells.[17] They may act against the human papillomavirus (HPV), which is considered a co-carcinogen.[18]

Types of Retinoids

Vitamin A is the term often used for various biologically active, related molecules. The term "retinoid" includes natural and synthetic forms that may or may not show activity similar to vitamin A.[13]

There are three generations of synthetic retinoids used in dermatology (Chart 1). [13]

The most commonly administered systemic retinoids in chemoprevention of skin cancer are: etretinate, acitretin and isotretinoin, the latter being widely used to treat severe acne since the 1980's.[6,9,19] These drugs have proven effective in inhibiting the development of new precancerous skin lesions and skin cancers in organ transplant recipients. Etretinate, due to its extremely long half-life, has been replaced by its active metabolite, acitretin, which has become the most widely used drug for this purpose. Although the use of oral isotretinoin in organ transplant recipients is limited, it is the most studied retinoid for the prevention of non-melanoma skin cancers in immunocompetent patients.[20] Due to its shorter half-life, isotretinoin is useful for women planning to become pregnant. The length of time after the discontinuation of the drug required for pregnancy is only one month, while for acitretin it is two years.[13,20]

The most commonly used topical retinoids are: tretinoin, adapalene, isotretinoin, tazarotene, retinol and retinaldehyde. Tretinoin, or all-trans retinoic acid, was introduced by Stuttgen in the treatment of skin diseases in 1959 (quoted in Torras, 1996).[8,21] Ten years later, Kligman, began to use it for the treatment of acne vulgaris.[22] In 1983, Cordero was the first to introduce it in the treatment of skin aging.[23] It was noted that the number of AKs decreased with the use of topical tretinoin for skin photodamage.[24] It is believed that the atypias in the epidermal keratinocytes are reversed and the density of Langerhans cells is increased, as occurs with the use of systemic retinoids.[24,25]

Chart 1: Synthetic retinoids

Retinoids	Examples	Administration route
First generation (non-aromatic)	Tretinoin Isotretinoin Alitretinoin	Topical Topical and systemic Systemic
Second generation (mono-aromatic)	Etretinate Systemic	Acitretin Systemic
Third generation (poly-aromatic)	Adapalene Tazarotene Bexarotene	Topical Topical Systemic

STUDIES ON THE USE OF SYSTEMIC AND TOPICAL RETINOIDS IN THE PREVENTION AND TREATMENT OF ACTINIC KERATOSES

The aim of most studies on chemoprevention with retinoids has been the prevention or treatment of non-melanoma skin cancers (SCC and basal cell carcinoma - BCC). The skin of individuals with these cancers generally has advanced or severe photodamage, with the visible presence of multiple, and possibly subclinical, AKs. Thus, some studies evaluated the activity of retinoids on the AKs as a secondary objective. Studies in which the primary objective was to evaluate the effect of retinoids on AKs, are listed in the last line of chart 2. [18,25-45]

There is a higher prevalence of studies involving systemic retinoids, acitretin and etretinate for AKs in conjunction with SCC and BCC, but topical retinoids are preferred when AKs are evaluated alone (Charts 2 and 3). [18,25-28,30,32,33,35-37,45]

Synthetic retinoids have been shown to be effective in reducing AKs and inhibiting the development of cancer.[27] Since organ transplant recipients are at increased risk of warts, AKs and non-melanoma skin cancers, many of the studies conducted the prevention of skin cancers and precancerous lesions have this group of patients as eligible population. [25,26,28,38]

In relation to controlled studies of systemic retinoids and AKs, Bavinck et al (1995) found that 13.4% of organ transplant recipients who used acitretin saw a reduction in the number of AKs, while in 28.2% of the placebo patients, there was an increase.[27] De Sevaux et al, (2003) compared two doses of acitretin in patients with AKs and observed a significant reduction in number in both groups after 2 months.[28] George et al (2002) used acitretin compared to placebo, but due to difficulty in counting lesions, they considered only patients with up to 10 AKs. They reported complete clearance of lesions in the treated group and an increased number of lesions in the control group.[35] Moriarty et al (1982) showed that etretinate was superior to placebo in reducing the number and size of AKs (84% of the etretinate group had complete or partial response compared to 5% in the placebo group). 18 Rook et al (1995) compared etritinate combined with tretinoin, separately. This is the only study to date that compares topical and systemic retinoids. 25 The effectiveness regarding the combination of oral and topical retinoids, versus topical retinoids, is difficult to establish in this clinical trial due to the small number of patients (N=11), the high dropout rate during the study (N=4), the short follow-up period and lack of a standard concentration for the topical retinoids in both groups.[25]

In contrast to topical retinoids, most studies on systemic retinoids and AKs are based around case series. Hughes et al (1988) used two doses of etretinate for 18 months. Of the 15 eligible patients, 13 had AKs and 2 had only BCCs. Only 12 patients with AKs completed the study, with an average reduction in the number of AKs before and after treatment of 12.73 to

Chart 2: Type of skin lesion evaluated according to each study using topical and/or systemic retinoids

Skin lesions	Author (year)	Retinoids
AK/SCC	Kelly (1991)[26] Bavinck (1994)[27] De Sevaux (2003)[28]	Etretinate; acitretin; acitretin
AK /BCC	Bollag (1970)[29]; Hughes (1998)[30]	Tretinoin etretinate
AK /warts	Euvrard (1992)[31]	Tretinoin
AK /warts/SCC	Rook (1995)[25]	Tretinoin x etretinate + tretinoin
AK /BCC/SCC	Majewski (1994),[32] Yuan (1995)[33] Euvrard (1998),[34] George (2002),[35] McNamara(2002)[36]	Isotretinoin + calcitriol acitretin; adapalene; acitretin; acitretin
AK /warts/BCC/SCC	Shuttleworth (1988),[37] McKenna (1999)[38]	Etretinate; acitretin
AK alone	Moriarty (1982),[18] Kligman (1991),[39] Misiewicz (1991),[40] Alizerai (1994),[41] Moglia (1997),[42] Campanelli (2002),[43] Smit (2002),[44] Smit (2004)[45]	Etretinate; tretinoin 0.05%; Ro-14-9706 x tretinoin 0.05%; isotretinoin 0.1%; retinoid fenretinide; retinaldehyde 0.05%; tretinoin 0.02% x calcipotriol; acitretin

5.82. 30 Kelly et al (1991), in a study geared towards the prevention of new non-melanoma tumors, mentioned that in the four patients treated with etretinate, there was improvement of the AKs during the use of the drug, with a low recurrence rate after interruption. In addition to the low number of patients, no objective method was used to measure reduction in AKs.[26] Majewski et al (1994) followed 12 patients to evaluate non-melanoma tumors and AKs. There was reduction in the number of AKs, ranging from 40% up to full clearance in patients with the lowest number of AKs before treatment.[32] McKenna et al (1999) and McNamara (2002), due to difficulty in counting the AKs, only mentioned a decrease with treatment, but did not specify the numbers.[36,38] Shuttleworth et al (1998) used etretinate, 1mg/kg daily for 6 months on a small number of organ transplant recipients. There was a reduction of new non-melanoma tumors but it remained unclear whether there was any improvement in the AKs. The authors noted complete clearance in 4 patients. However, they fail to specify whether the clearance concerned the viral, actinic or carcinomatous lesions.[37] Smit et al (2004) carried out a clinical trial, which yielded results that were different from those of previous studies. They used acitretin at a dose of 0.4 mg/kg/day for 3 months, and concluded that the drug reduced significantly epidermal thickness, improved the appearance of AKs by altering keratinization and resulted in stratum corneum desquamation. The study was based on histopathological and immunohistochemical findings.[45]

There are studies which evaluate the effect of topical retinoids on prevention and treatment of AKs (Chart 4).[25,29,31,34,39-44,46]

The advantage of using topical retinoids is systemic toxicity avoidance, although there may be local adverse effects which vary with drug concentration. Good results are obtained in treatment and chemoprevention of AKs in immunocompetent patients, particularly with topical tretinoin and isotretinoin, which is why the eligible population for topical retinoids are immunocompetent in most of the studies.[20] In a controlled study, Alizerai et al (1994) evaluated the effect of isotretinoin cream 0.1% compared to placebo in 100 patients, and demonstrated a significant decrease in AKs on the face, but no real improvement on the scalp and arms.[41] Euvrard et al (1992) demonstrated AK reductions of 45% versus 23%, in the tretinoin 0.05% group versus placebo, respectively.[31] Kligman et al (1991) conducted the largest controlled study on retinoids for AKs and demonstrated that tretinoin 0.1%, compared to the placebo, was effective in reducing AKs when applied twice daily, with excellent responses in 73% of patients.[39] Misiewicz et al (1991) compared the efficacy and tolerability of the retinoid Ro 14-9706 to tretinoin 0.05% ointment used for 16 weeks. Areas treated with Ro 14-9706 showed a decrease of 37.8% in AK number, while in areas treated with tretinoin, the decrease was 30.3%. Compared to pre-treatment numbers, the decrease was significant but there was no difference between the two drugs, although Ro 14-9706 was better tolerated.[40] Euvrard et al (1998) compared different concentrations of adapalene, revealing a significant reduction in AK number of 32% versus 21%, with concentrations of 0.3% and 0.1% respectively. 34 Only one study showed no difference in terms of retinoid use concerning reduction in AK numbers, in all the groups analyzed (0.02% tretinoin, 0.02% tretinoin combined with calcipotriol, calcipotriol and emollient). There were no clinical or histological changes after 6 weeks, though the authors explained that the follow-up period may have been too short for such an examination.[44]

Regarding the case series on the use of topical retinoids for AKs, Bollag et al., 1970, observed a 50% reduction of AKs on arms and hands with tretinoin 0.1% and 0. 3%.[29] Campanelli et al (2002) found no difference in the use of 0.05% retinaldehyde, for 6 to 142 months, in immunocompetent patients. As the study was not controlled, its value is limited.[43] Moglia et al (1996) treated 18 patients with facial AKs with the retinoid fenretinide, twice a day, for 3 months. Complete and partial regression was observed in 56% and 44% of patients, respectively. However, 44% of patients developed new lesions 3 months after cessation of treatment.[42]

When the clinical trial is not controlled, one factor of bias linked to the efficacy of the analysed drugs is sunscreen. Two papers indicate that suncreens can diminish the number of AKs by up to 25% in immunocompetent patients, and 50% in organ transplant recipients, which could enhance other treatments.[47,48]

SIDE EFFECTS OF SYSTEMIC RETINOIDS

The side effects of systemic retinoids are divided into: 1) pharmacological effects such as skin xerosis, cheilitis, dry eyes, conjunctivitis, nasal dryness, epistaxis and irritant dermatitis and 2) toxic effects that are unpredictable, rare, reversible, dependent on individual susceptibility and predisposing factors (obesity, alcoholism, diabetes mellitus, hypertension, smoking), such as elevated liver enzymes, increased levels of triglycerides and cholesterol, increased LDL fraction and decreased HDL fraction.[49,50]

Teratogenicity is the most serious adverse and irreversible (drug category X) effect. Any exposure, regardless of dose, at any time during pregnancy, but especially in the first trimester, may be teratogenic.[51] This justifies controlling the risk of pregnancy by using two safe contraceptive methods and starting

Chart 3: Studies involving systemic retinoids in prevention and treatment of actinic keratoses, in chronological order

Author (year)	Study design Nº patients	Drug and treatment duration	Results
Moriarty (1982)18	Cross-over, open, randomized, controlled; 50 immunocompetent patients	Etretinate 5mg 3x/day versus placebo, 2months, after, the groups were swapped for 2 more months (placebo x etretinate)	84% of the etretinate group had complete or partial response compared to 5% in the placebo group
Shuttleworth (1988) 37	Cases series 6 transplanted patients	Etretinate 1mg/kg/day, 6months	"Almost" complete resolution of neoplastic and pre-neoplastic lesions in 4 patients, partial response in 1 patient
Kelly (1991)26	Cases series 4 transplanted patients	Etretinate 50mg/day, 8-13months	AKs were not counted but they became less severe after treatment
Bavinck (1995)27	Double-blind, randomized, controlled 44 transplanted patients	Acitretin 30mg/ day versus placebo, 6 months	13.4% of patients in the acitretin group saw decreases in the number of AKs, while in the placebo group, 28.2% of the patients saw increases
Majewski (1994)32	Cases series 4 immunocompetent patients	Isotretinoin 0.4-0.5mg/kg/day + calcitriol 0.5-1µg, 12months, approximately	Patient 1- complete clearance; Patients 2 and 3- AK regression about 50 to 80%; Patient 4 – regression of 40% of AKs in number and size
Yuan (1995)33	Cases series 15 transplanted patients	Acitretin 10-50mg/day, 6-12 months	The number of skin cancers decreased in 4 of the 6 patients. All warts and AKs had improvement in all patients (without counting)
Rook (1995)25	Open, non-randomized, controlled 11 transplanted patients	Group 1= 7 patients (tretinoin 0.025% to 0.05% according to tolerance) + (etretinate 10mg/day or alternate days), 6 months according to improvement in AKs Group 2= 4 patients (tretinoin 0.025 to 0.05%, according to tolerance)	Both groups obtained a decrease in the number of AKs and an improvement in the number of Langerhans cells. Four patients in the combined group obtained almost 50% regression of AKs while 2 in the tretinoin group obtained improvement, after six months
Hughes (1998)30	Cases series 15 immunocompetent patients	Etretinate,18 month follow-up 1st month – 1.5mg/kg/day 2nd and 3rd months – 0.75mg/kg/day	Only 12 patients with AKs completed the study, with an average reduction in the number of AKs before and after treatment of 12.73 to 5.82
McKenna (1999)38	Cases series, 16 transplanted patients	Acitretin 0.3mg/kg/day, 5 years	There was significant improvement in warts and AKs, but they were not counted
George (2002)35	Cross-over, open, randomized controlled 23 immunocompetent patients	Group 1: Acitretin 25mg/day (variable) + placebo, 12months Group 2: Placebo + Acitretin 25mg/day (variable), 12months	In the acitretin group, complete clearance or reduction in number of AKs occurred in all patients, except one. In the placebo group, there was an increase of 50% in the number of AKs in 3 patients and 6 remained with no significant change
McNamara (2002)36	Cases series 5 transplanted patients	Acitretin 10 or 25mg/day, 10-24 months	AKs seemed to be in varying degrees of resolution with treatment but they were not counted
De Sevaux (2003)28	Open, randomized controlled 26 transplanted patients	Acitretin Group 1: 0.4mg/kg/ day, 12 months Group 2: 0.4mg/kg/ day, 3 months + 0.2mg/kg/ day, 9 months	Significant reduction in number of AKs in both groups after 2 months, but no difference between the groups at any particular point
Smit (2004)45	Cases series 33 transplanted patients	Acitretin: up to 0.4mg/kg/ day, 3months (biopsy of AKs)	Reduction of 44% in epidermal thickness due to stratum corneum, no difference in expression of p53 and Ki67 and an increase in the expression of K13 and K19 after treatment with acitretin

CHART 4: Studies on the use of topical retinoids (tretinoin, adapalene and isotretinoin) in prevention and treatment of actinic keratoses, in chronological order.

Author (year)	Study design Nº patients	Drug and treatment duration	Results
Bollag (1970)29	Case series 60 immunocompetent patients	Tretinoin 0.1% and 0.3% cream, 2x/day, in AKs and 1x/day, occlusive in BCCs, 3 to 8 weeks	44 patients showed total or more than 50% of regression of the AKs. Tretinoin 0,3% showed higher rates of regression, as well as the face, compared to the upper limbs
Purcell (1986)46	Double-blind, non-randomized, controlled; 24 immunocompetent patients (8 drop out)	Tretinoin 0.05% ointment x placebo, 12months	There was no statistically significant difference between the groups in relation to the number of AKs
Kligman (1991)39	Double-blind, controlled 1265 immunocompetent patients (multicentered)	Tretinoin 0.05% x tretinoin 0.1% x placebo ointment, up to 15 months	The most effective treatment for reducing AKs was 0.1% tretinoin, applied twice daily (P.001). An excellent response was observed in 73% of tretinoin-treated patients compared with only 40% of placebo
Misiewicz (1991)40	Double-blind, randomized, controlled, 25 immunocompetent patients	Ro 14-9706 x tretinoin 0.05% ointment, 16 weeks	Decrease of 37.8% in AK numbers with Ro 14-9706, while with tretinoin, the decrease was 30.3%. There was no difference between the two drugs, although Ro 14-9706 was better tolerated
Euvrard (1992)31	Double-blind, randomized, controlled, 22 transplanted patients	Tretinoin 0.05% ointment x placebo, 3 months	Reduction of 45% versus 23% of AKs in the tretinoin 0.05% group versus placebo, respectively
Alizerai (1994)41	Double-blind, randomized, placebo-controlled 100 immunocompetent patients	Isotretinoin 0.1% ointment, 2x/day x placebo, 24 weeks	66% of the patients with isotretinoin versus 45% of the patients with placebo had a partial or complete response, whereas 34% of patients with isotretinoin versus 55% of patients with placebo had no response or worsening on the face
Rook (1995)25	Open, non-randomized, controlled 11 transplanted patients	Group 1= 7 patients (tretinoin 0.025% to 0.05% according to tolerance) + (etretinate 10mg/day or alternate days), 6 months according to AK improvement, Group 2= 4 patients (tretinoin 0.025 to 0.05%, according to tolerance)	Both groups obtained a decrease in the number of AKs and an improvement in the number of Langerhans cells. Four patients in the combined group obtained almost 50% of regression of AKs, while 2 in the tretinoin group obtained improvement, after six months
Moglia (1997)42	Case series 18 immunocompetent patients	Retinoid fenretinide 2x/day, 3months	Complete and partial regression was observed in 56% and 44% of patients, respectively
Euvrard (1998)34	Randomized, controlled 40 transplanted patients	Adapalene 0.1% x adapalene 0.3%, 6 months	Reduction of 32% versus 21% in AKs number with concentrations of 0.3% and 0.1% respectively
Campanelli (2002)43	Case series 61 immunocompetent patients	Retinaldehyde 0.05%, 6-142 months	37% of the patients aged over 60 and 10% between 41-60 years developed AKs during the treatment. Retinaldehyde alone does not appear to have prophylactic effects on the development of AKs
Smit (2002)44	Open, non-randomized, controlled, 13 immunocompetent patients	Group 1: Tretinoin 0,02% Group 2: calcipotriol Group 3: both Group 4: emollient All 2x/day, 6 weeks	There were no significant differences in clinical, histological and immunohistochemical parameters between the four different therapies during a 6-week treatment period.

treatment after menstruation.[52]

The occurrence of depression, suicidal thoughts or suicide attempts possibly caused by oral isotretinoin in the treatment of acne vulgaris, has been documented in the form of case reports, population and case-control studies. The incidence observed varies from less than 1% to 3%, while in the general population it is estimated to be between 1.6 to 7.5%, with an average of 3% 53-55 However, to date, no conclusive epidemiological or pharmacological evidence has been detected that could explain this association.[56-57] Instead, assessments of quality of life have shown improvement in rates and reduction in depressive symptoms, in patients treating acne with oral isotretinoin.[54] Other previously described, but very rare, side effects, are: headaches, joint pain, bone disorders, leukopenia, anemia, etc. Recently, the risk of developing inflammatory bowel disease, particularly ulcerative colitis, has been reported during the use of oral isotretinoin. However, population and case control studies have not confirmed this assumption.[58,59]

SIDE EFFECTS OF TOPICAL RETINOIDS

Topical retinoids cause only local reactions such as erythema, scaling, burning and irritation.[60] Most of these effects are seen to reach a peak during the first week and decrease over time.[61] Higher concentrations, e.g. 0.1%, are related to increased frequency of adverse events.[62]

DISCUSSION

Unlike some studies published on the ineffectiveness of retinoids for the prevention of non-melanoma skin tumors and AKs, it is clear that most research demonstrates the efficacy of that class of drugs with regard to AKs (Charts 3 and 4).[28,41,44,46,63-65]

However, most of the studies are case series with small numbers of patients; in four controlled studies, there was no randomization and in others there was no adequate explanation about method. Other limiting factors are sample sizes and high dropout rates 25 The lack of standardization for topical and oral retinoid concentrations, and treatment time, are problems that must be highlighted, particularly in those studies that point out the ineffectiveness of retinoids in the treatment and prevention of AKs and non-melanoma skin tumors.[44,46]

As noted in chart 2, the main focus of some authors was not AKs but non-melanoma skin cancers, which somehow affected the clinical outcome for AKs. Indications for chemoprophylaxis with oral retinoids, according to Otley et al, only involve AKs when they are accompanied by the current or previous presence of non-melanoma skin tumors, which may explain the small number of articles involving oral retinoids and AKs.[66] Some publications mention a decrease in AKs without establishing a statistical value, and justify this by the difficulty of counting these lesions, raising a further problem for clinical studies involving AKs

The outcomes of clinical studies involving AKs are a great problem. Most are based on lesion counts before and after treatment in absolute numbers or by category. Others refer to an apparent reduction but do not provide numbers.[36,38] Counting AKs is still the most widely used method although the results may be highly questionable due to many difficulties, since they can be subclinical, ill-defined, multiple, confluent and similar to other conditions (seborrheic keratoses, warts). In addition, other significant factors are: diagnostic disagreement, insufficient training of observers in counting lesions, dry skin in the elderly, appearance of new lesions and spontaneous regression. Although it is far from ideal method, there is currently no better alternative to counting.[67-69]

The concept that AKs are premalignant disorders has been supported by several studies, and genetic mutations are present simultaneously in AKs and SCC.[70,71] Thus, AKs can be considered a clinical model of carcinogenesis. As they are extremely frequent in dermatological clinical practice, clinical trials regarding prevention and treatment of AKs should be considered in the study of cutaneous carcinogenesis chemoprevention.[72]

FINAL REMARKS

In our opinion, blind, randomized and controlled trials with adequate sample sizes aimed specifically at actinic keratoses, are needed to clarify the real benefit of topical and/or oral retinoids. We consider it important that new models be developed in relation to methodology and outcomes. Comparison of efficacy and safety between oral and topical retinoids in the prevention and treatment of non-melanoma skin cancers and AKs, is an essential prerequisite for the establishment of new strategies to control these conditions. ❑

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